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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/152,698	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,71,75,76,85-89,93,95,96 and 98-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,71,75,76,85-88,93,95,96 and 98-115* is/are rejected.

7)☐ Claim(s) *89* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 27, 2004 has been entered.

2. Claims 73, 74, 91, 92 and 94 have been canceled. Claims 85, 93, 95, 99, 100, 104-112 and 115 have been amended. Claims 30, 71, 75, 76, 85-89, 93, 95, 96 and 98-115 are pending and under consideration.

3. Claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al ('Cancer Immunotherapy' In: Advances in Cancer Research, 1992, vol. 59, pp. 245-323) in view of Crowley et al (Journal of Experimental Medicine, 1990, vol. 172, pp. 383-386) and Steinman et al (WO 93/20185) and Sallusto et al (Journal of Experimental Medicine, 1994, vol. 179, pp. 1109-1118) and de La Salle et al ('FcgR on Human Dendritic Cells' In:Human IgG Receptors, 1996, pp. 39-55, Van de Winkel et al Eds), and Schwartz ('Cancer Markers' In: Cancer: Principles and Practice of Oncology, 4th Edition, vol. 1, 1994, DeVita et al, Ed.s., page 531-542, cited in a previous Office action) and Vrba et al (PNAS, 1975, Vol. 72, pp. 4602-4606) and Paul (Fundamental Immunology, (text), 1993, page 1163) and the abstract of Jurncic-Winkler et al (Eur Urol, 1993, Vol. 24, pp. 487-491) and Simitsek et al (J Exp Med, 1995, Vol. 181, pp. 1957-1963).

Kedar et al teach that tumor cell populations are heterogeneous comprising cells with variable sensitivities to immunological effector mechanisms. Kedar et al teach that tumor samples collected from a individual often react differently with antibodies and CTL clones. Kedar et al teach that "cocktails" of different antibodies and/or several T-cell clones directed against different antigenic epitopes of the tumor may be required for control of the tumor. (page 255, section C under the heading of "Heterogeneity of the Tumor Cell Population").

Crowley et al teach that peptide fragments of proteins are endocytosed by antigen-presenting cells and then bound to MHC products on the surface of said antigen-presenting cells

(page 383, first column, lines 1-5). Crowley et al teach that when antigens are administered to animals and the dendritic cells of said animals are isolated, said dendritic cells are carrying the antigen in an immunogenic form (page 383, first column, lines 7-9). Crowley et al teach that when myoglobin was administered to mice, the dendritic cells taken from said mice were able to activate three different T-cell clones (Table 1: H-2d + myoglobin).

Steinman et al teach that dendritic cells are termed "nature's adjuvant" because aid cells are capable of directly priming T cells that recognize only antigens presented by the particular MHC class of the presenting dendritic cell and because dendritic cells are capable of capturing antigens in an immunogenic form in situ (page 33, lines 16-23). Steinman et al include tumor antigens as the antigens presented by dendritic cells (page 33, lines 14-16). Steinman et al teach that dendritic cells are capable of processing complex antigens into those peptides that would be presented by self MHC products (page 33, lines 29-31).

Sallusto et al teach that the efficiency of soluble antigen presentation by dendritic cells can be enhanced by specific antibodies via Fc Receptor-mediated antigen uptake (title and abstract, lines 8-10). Sallusto et al teach that dendritic cells have pinocytic activity and that the Fc receptor II on dendritic cells can be used to increase the uptake of antigen in antigen-antibody complexes (page 1110, first column, lines 11-13) which results in antigen-presentation and stimulation of naive T-cells (page 1110, first column, lines 5-6 and lines 13-16). Sallusto et al teach that dendritic cells were the most effective of the antigen-presenting cells at presenting a soluble antigen and that in the presence of the antibody that binds to said antigen presentation increased 100-fold (page 1111-1112, under the heading "Efficient presentation of soluble Antigen and Antibody-antigen complexes by Immature Dendritic Cells" and page 1115, second column, lines 16-20).

De la Salle et al teach that presentation of exogenous soluble antigens to helper T-cells is a complex process which requires uptake of proteins by antigen presenting cells, digestion of said proteins into immunogenic peptides, the intracellular association of the immunogenic peptides with MHC II molecules and the transport of the resulting immunogenic complexes to the plasma membrane for recognition by antigen specific T-cells (page 46, lines 20-26). De la Salle et al teach that targeting of antigens to Fcgamma Receptor on Langerhans cells by means of immune complexes comprising IgG complexed to its target soluble antigen resulted in antigen

presentation at dramatically reduced levels of soluble antigen and that this process required both the uptake of immune complexes via the Fcgamma receptor and the processing of the antibody-complexed soluble antigen by the Langerhan's cells (page 46, lines 37-45).

Schwartz teaches tumor markers that are shed into the serum of cancer patients having breast, ovarian, prostate and gastro-intestinal cancers (Table 21-5). These markers include PSA.

The abstract of Jurncic-Winkler et al teaches that PSA consists of multiple epitopes.

Vrba et al teach that CEA consists of multiple antigenic determinant (page 4604, first column, 3rd full paragraph).

Simitsek et al teach that the presence of an antibody on a processed antigen can both suppress and boost the presentation of antigenic determinants that fall within the "footprint" of the antibody (page 1957, second column, lines 4-7 and page 1958, second column, under the heading of "Simultaneous Boosting and Suppression of Different T Cell Determinants" and page 1959, first column, under the heading "The Footprinting of the 11.3 antibody Includes bith Suppressed and Boosted Determinants" and page 1961, second column, lines 7-9 under the heading of "Discussion"). Simitsek et al teach that T cells specific for such subdominant or cryptic epitope exist and are capable of being activated (page 1962, second column, lines 15-19). Simitsek et al teach that enhanced loading onto class II MHC complexes as a result of this modulation is a novel mechanism revealing otherwise cryptic T-cell determinants to which tolerance has never been established (page 1962, lines 23-29).

It would have been prima facie obvious at the time the invention was made to stimulate an immune response against more than one epitope of a tumor associated antigen by administering to a patient having a tumor a soluble complex of a tumor -associated antigen complexed to an antibody or antigen binding fragment thereof comprising an Fc region. One of skill in the art would have been motivated to do so by the teachings of

1. Kedar et al on the desirability of having several T-cell clones directed against different antigenic epitopes of the tumor may be required for control of the tumor;
2. Crowley et al on the ability of dendritic cells exposed in vivo to exogenous antigen to present multiple immunogenic epitopes to T-cells;
3. Steinman et al on the capability of dendritic cells to processing complex antigens into those peptides that would be presented by self MHC products;

4. Sallusto et al on the enhancement of soluble antigen presentation by dendritic cells through the uptake of antigen-antibody complexes;

5. De La Salle et al on the enhancement of soluble antigen presentation by Langerhan's cells by antigen-antibody complexes and the required processing of the antigen within the antigen-antibody complex after uptake via the Fc receptor of the dendritic cell;

6. Schwartz on tumor antigens which are shed from breast, ovarian, prostate and gastro-intestinal tumors and present as soluble antigens in the serum of cancer patients.

One of skill in the art would recognize after reading of the above prior art references, that dendritic cells are capable of taking up soluble antigen in the form of antigen-antibody complexes in a process that involves internalization from the Fc receptor which is separate from the process of uptaking particulate antigens, and that antigens which are internalized by dendritic cells are processed into immunogenic fragments which are presented on the surface of said dendritic cell. One of skill in the art would also recognize that if a complex exogenous antigen were internalized by a dendritic cell more than one immunogenic epitope can be presented to a T-cell, such as was illustrated in the teachings of Crowley et al. One of skill in the art would be motivated to provide more than one immunogenic epitope of a tumor associated antigen in order to activate more than one T-cell against said antigen after reading the teachings of Kedar et al on the desirability of having several T-cell clones and antibodies directed against different antigenic epitopes of the tumor in order to circumvent the problem of antigenic heterogeneity exhibited by a tumor mass. It would have been further obvious at the time the claimed invention was made that the presence of the antibody on the antigen can provide a means for activating T-cells to subdominant epitopes or cryptic epitopes to which tolerance has never been established. One of skill in the art would understand that because of the size of soluble tumor markers such as CEA, and PSA, there is reasonable expectation that modulation of antigen processing by means of an antibody would enable the loading of MHC II with a T-cell determinant to which tolerance has never been established. One of skill in the art would be motivated to provoke an immune response using a determinant to which tolerance has never been established by the teaching of Paul indicating that tolerance is a means by which tumor cells evade immune detection.

4. Claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz and Vrba et al and Paul and the abstract of Jurncic-Winkler et al and Simitsek et al as applied to claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 101, 103-110 and 113-115 above, and further in view of Schlom ('Monoclonal Antibodies: they're more and less than you think', In: Molecular Foundations of Oncology, 1991, pp. 95-133, cited in a previous Office action).

The prior art references renders obvious methods of treating oncological disease and methods of stimulating a multi-epitopic response to a tumor associated antigen comprising the administration of a soluble complex comprising a tumor associated antigen and a monoclonal antibody having a Fc region for the reasons set forth above. Claims 71 and 86 are further drawn to a single-chain antibody, a humanized antibody and a chimeric antibody.

The combination of the references does not specifically address humanized or chimerized antibodies in the soluble complex.

Schlom teaches that HAMA response develop in more than 90% of patients receiving more than three doses of a monoclonal murine Antibody and that it is unrealistic to assume that one or two doses or a given anti-cancer therapeutic would be effective. Schlom concludes that because of the HAM response only the first and perhaps the second administration of the antibody actually reached the tumor site in a therapeutically effective amount. Schlom teaches the use of recombinant chimeric antibodies contain a human Fc region to avoid the HAMA response (page 98 second column, second full paragraph to page 99, first column, first paragraph).

It would have been prima facie obvious at the time the invention was made to use humanized or chimeric antibodies comprising a human Fc region for the administration to humans of the soluble complexes rendered obvious by the combination of Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz. One of skill in the art would be motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response in patients undergoing immunotherapy for cancer, and the teachings of Schlom on the avoidance of the HAMA response by the administration of antibodies having a human Fc domain.

5. Claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 99, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz and Vrba et al and Paul and the abstract of Jurncic-Winkler et al and Simitsek et al as applied to claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 101, 103-110 and 113-115 above, and further in view of Dong et al (In: Vaccine Design: The Subunit Approach, Powell et al, Ed., 1995, pp. 625-643).

Claim 99 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is administered with an adjuvant.

The combination of Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz does not specifically teach the administration of a cytokine as an adjuvant.

Dong et al teach cytokines as vaccine adjuvants. Dong et al teach that cytokines both increase the number of antigen-presenting cells that can present antigens, and activate said antigen presenting cells (page 626, last sentence).

It would have been prima facie obvious at the time the claimed invention was made to administer the soluble complex with a cytokine as an adjuvant. One of skill in the art would be motivated to do so by the teachings of Dong et al on the use of cytokines as adjuvants to stimulate antigen presentation and activate antigen presenting cells.

6. Claims 30, 71, 75, 76, 85-88, 93, 95, 96, 98, 101-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz and Vrba et al and Paul and the abstract of Jurncic-Winkler et al and Simitsek et al as applied to claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 101-110 and 113-115 above, and further in view of O'Brien (US 5,976,818) and Baum et al (Cancer Research, 1994, vol. 73, 3 suppl., pp. 1121-1125, cited in the previous Office action).

Claim 88 embodies the composition of claim 87 wherein the monoclonal antibody is produced by the hybridoma having the ATCC deposit number PTA-1883. the specification identifies said deposited hybridoma as producing the B43.13 antibody. Claim 102 embodies the method of claim 101 wherein the ovarian associated antigen is CA125.

O'Brien teaches that CA125 is an ovarian tumor antigen in the extracellular matrix of CA-125 .
producing cells (abstract) , ascites fluid and tumor serum (column 4, line 3). It can be concluded that CA 125 is a shed tumor antigen.

Baum et al teach that the B43.13 antibody binds to CA-125 of ovarian cancer cells (page 1122, first column, under the heading "Monoclonal Antibodies").

It would have been prima facie obvious to one of skill in the art at the time the invention was made to use a complex of B43.13 bound to CA-125 to alter the immunogenicity of Ca-125 and treat ovarian cancer. One of skill in the art would have been motivated to do so by the teachings of O'Brien on CA-125 as a tumor antigen found in the serum and ascites of patients having an ovarian tumor. One of skill in the art would have concluded that CA-125 is a shed antigen and is soluble in the serum and ascites, and is therefore present as a circulating tumor antigen. One of skill in the art would also conclude that the B43.13 antibody bound an epitope of CA-125 that was antigenically exposed on the tumor antigen and therefore a complex between B43.13 and shed CA-125 could be formed.

7. Claims 30, 71, 75, 76, 85-87, 93, 95, 96, 98, 100-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz and Vrba et al and Paul and the abstract of Jurncic-Winkler et al and Simitsek et al as applied to claims3 0, 71, 75, 76, 85-87, 93, 95, 96, 98, 101-110 and 113-115.

Claim 100 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of from about 0.1 ug to about 2 mg per kilogram of body weight of the host. Claim 111 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of about 2 mg per host. Claim 112 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of about 0.1 ug to about 200 ug per kilogram of body weight of the host.

None of the aforesaid prior art references teaches or suggests the specific dosages claimed. however, it is recognized in the art that the establishment of optimal dosages is empirical but within the purview of one of skill in the art.

It would have been prima facie obvious to optimize the dosage of antigen-antibody complexes used in the claimed methods to the recited values and ranges. One of skill in the art would have been motivated to do so in order to most effectively treat individuals having tumors.

8. Applicant argues that the use of the complex of the tumor associated antigen gave unexpected results because the immune response was surprising more robust than the use of the tumor antigen not in a complex. This has been considered but not found persuasive. The prior art teaches that greater antigen presentation is afforded by antigen-antibody complexes rather than antigen alone. It is not surprising that the immune response is heightened because the increase in antigen presentation would be expected to dramatically increase. Applicant argues that the combination of references fails to reasonable suggest that complexes comprising tumor associated antigens would have any particular benefit. This is not persuasive as the art teaches that exposure of antigen presenting cells to antibody-antigen complexes results in a much greater presentation of antigen by said APC. For instance Sallusto et al teach that the efficiency of soluble antigen presentation by dendritic cells can be enhanced by specific antibodies via Fc Receptor-mediated antigen uptake.

9. Claim 89 remains objected to for being dependent upon rejected subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
2/7/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER